REMARKS

Claim 36 has been amended. No new matter has been added. Claims 36-39 are pending in this application.

Rejections under 35 U.S.C. § 112

Rejections under 35 U.S.C. § 112, 2nd paragraph

A. Claim 36 stands rejected under 35 U.S.C. § 112, 2nd paragraph, as allegedly being indefinite. Specifically, the Office Action asserts that the term "... on said substrate ..." is unclear as to how the reaction product is oriented with respect to the substrate and as to how the reaction product is attached to the substrate.

The rejection of claim 36 under 35 U.S.C. § 112, 2nd paragraph, has been obviated by amendment. As amended, claim 36 recites that the reactant ligand is immobilized on the substrate of the protein chip. The immobilization of a reactant ligand on a substrate is described in the specification, at least at p. 38, line 7 through p. 51, line 14.

It is noted for the record that the specification describes both the direct immobilization of a reactant ligand to a substrate and the indirect immobilization through chemical groups that are inert towards the fusion polypeptide. For example, pages 47-48 illustrate one compound that can be immobilized directly to an activated surface (p. 47, line 10 through p. 48, line 2) or that can be immobilized through the interaction of a disulfide group with the surface (p. 48, lines 4-9). In addition, the direct or indirect immobilization of the reactant ligand to the substrate does not prevent the fusion polypeptide portion of the reaction product from being in close proximity to the substrate. Thus, applicants respectfully traverse the Office Action's interpretation of the phrase "... on said substrate ..." as being limited to a reaction product that is adjacent to and/or directly attached to the substrate.

B. Claims 37-39 stand rejected under 35 U.S.C. § 112, 2nd paragraph, as allegedly being indefinite. Specifically, the Office Action asserts that it is unclear whether the moieties of formulas (X), (XI), and (XII) are covalently bound to the surface.

The Office Action also asserts that it is unclear what moiety on the surface these moieties could be attached to.

The rejection of claims 37-39 under 35 U.S.C. § 112, 2nd paragraph, has been obviated by amendment. Claims 37-39 depend from claim 36, which has been amended to recite that the reactant ligand is immobilized on the substrate. The moieties recited in claims 37-39 each include the group " –Z ", which comprises the reaction product recited in claim 36. Thus, claims 37-39 cover specific examples of reaction products containing a reactant ligand immobilized on the surface of a substrate.

With respect to claim 37, the reaction product is recited as immobilized through the interaction of the gold surface with the sulfur atom in formula (X). Claims 38 and 39 are not limited to examples in which there is a direct linkage between the surface and the " –Q– " group (claim 38) or the " –L– " group (claim 39), and do not preclude the presence of other chemical groups between the recited formulas and the surface.

C. Claims 36-39 stand rejected under 35 U.S.C. § 112, 2nd paragraph, as allegedly being indefinite. Specifically, the Office Action asserts that the term "... a reaction product of a reactant ligand and a fusion polypeptide ..." as recited in claim 36 is unclear. The Office Action further asserts that the specification inadequately describes the reaction between the reactant ligand and the capture polypeptide and the resultant bond formed.

The rejection of the claims under 35 U.S.C. § 112, 2nd paragraph, with respect to the term "... a reaction product of a reactant ligand and a fusion polypeptide ..." is respectfully traversed. Contrary to the assertion in the Office Action at p. 2, section 3)c), the description of reactant ligands, capture polypeptides, and their reaction products in the specification is not limited to a single paragraph. Rather, these two moieties and their reaction products are described both generically and specifically at least at p. 13, line 8 through p. 17, line 25; and at p. 31, line 3 through p. 35, line 21. The chemical nature of bonds that may be formed in these reactions is described in a variety of ways, including half-life, inhibition constant, and rate constant of inhibition. In addition, specific examples are provided in the "EXAMPLES" section of the specification, beginning at p. 57. For example, inhibition studies are reported for the

binding of one reactant ligand with glutathione-S-transferase (GST; p. 60, lines 4-13; and p. 64, line 4 through p. 65, line 9), and of another reactant ligand with cutinase (p. 68, lines 1-21; and p. 71, line 11 through p. 72, line 24). The specification, when reviewed in its entirety, adequately describes reaction products between reactant ligands and fusion polypeptides, both generically and specifically.

In view of the above, claims 36-39 are in full compliance with 35 U.S.C. § 112, 2nd paragraph. Applicants request that the 35 U.S.C. § 112, 2nd paragraph rejections be withdrawn.

Rejections under 35 U.S.C. § 112, 1st paragraph

Claims 36-39 stand rejected under 35 U.S.C. § 112, 1st paragraph, as allegedly failing to comply with the enablement and written description requirements. Applicants note that the enablement requirement of 35 U.S.C. § 112, 1st paragraph, is separate and distinct from the written description requirement (MPEP 2161 and 2164). However, the second sentence of this section of the Office Action (p. 3, section 4) is directed to the definition of the enablement requirement only, and the individual rejections recite the phrase "enabling written description." There are no statements in these rejections that refer separately to the written description requirement. Accordingly, Applicants are responding to these rejections in the context of the enablement requirement only.

A. Claims 36-39 stand rejected under 35 U.S.C. § 112, 1st paragraph, as allegedly not enabled by the specification with respect to making a protein chip as claimed, and specifically with respect to immobilizing reactant ligands. The Office Action asserts that the specification does not:

> ... provide an enabling written description to support **any method of preparation** of the protein chips of the instant claims.
> [p. 3, section 4)a); emphasis added]

With reference to p. 38, lines 3-30 and to p. 8, lines 8-9 of the specification, the Office Action further asserts that only generic methods of immobilizing reactant ligands are

provided in the specification. The Office Action also notes that claim 36 as filed includes fusion polypeptides that are immobilized on the surface.

With respect to the issue of immobilization of a fusion polypeptide directly to a surface, the rejection has been obviated by amendment. As noted above, amended claim 36 recites that the reactant ligand is immobilized on the substrate of the protein chip. The immobilization of a reactant ligand on a substrate is described in the specification, at least at p. 38, line 7 through p. 51, line 14.

With respect to the issue of specific examples of immobilization of reactant ligands, the rejection is respectfully traversed. As noted above, the specification contains numerous specific examples of a variety of immobilized reactant ligands, the reaction of these reactant ligands with polypeptides, and the resultant immobilization of the reaction products. See, for example, the disclosure of self assembled monolayers (SAMs) at least at p. 39, line 23 through p. 42, line 24. This section provides a general description of the synthetic methods that may be used to link a group " –T " containing a reactant ligand to an alkanethiol or a disulfide, including specific reagents and protecting groups. Additional specific examples of immobilizations, including reaction schemes, are provided throughout the specification, for example at p. 42, line 25 through p. 51, line 14; and in the "EXAMPLES" section, for example at p. 61, line 3 through p. 65, line 9; p. 68, line 23 through p. 72, line 24; and p. 73, line 20 through p. 75, line 2.

The specification provides both generic and specific disclosure of the immobilization of reactant ligands, immobilization of the reaction products of reactant ligands with fusion proteins, and the use of these immobilizations in the preparation of protein chips as recited in the claims. The disclosure includes both general teachings and specific working examples and experimental data. Accordingly, claims 36-39 are in full compliance with 35 U.S.C. § 112, 1st paragraph, and applicants request that this rejection be withdrawn.

B. Claims 37-39 stand rejected under 35 U.S.C. § 112, 1st paragraph, as allegedly not enabled by the specification with respect to the moieties on the surface of the substrate. The Office Action asserts that the specification does not enable the direct attachment of a reaction product to a surface through a $-CH_2-$ group or other group lacking "significant length."

The rejection of claims 37-39 under 35 U.S.C. § 112, 1st paragraph, is respectfully traversed. The group " –Z " recited in claims 37-39 is recited as comprising the reaction product and does not exclude the presence of other atoms or chemical groups between the reaction product and the " –Q– " group. In addition, as noted above, claims 38 and 39 are not limited to examples in which there is a direct linkage between the surface and the " –Q– " group (claim 38) or the " –L– " group (claim 39), and do not preclude the presence of other chemical groups between the recited formulas and the surface.

Even in the instances where " –Q– " and/or " –L– " are $-CH_2-$ groups or other small groups, the specification provides specific disclosure. For example, reaction schemes are provided for the direct immobilization of three separate reactant ligands at p. 42, line 25 though p. 48, line 2. These reactant ligands may be immobilized directly through an ethyl carboxylate group ($-(CH_2)_2-C(O)O-$; pp. 44 and 46) or through an amine linkage (–NH– ; p. 48). In another example, a reaction scheme is provide for a reactant ligand to be immobilized through a thiol group having a hydrocarbon spacer of variable length (p. 48, lines 3-6). Applicants respectfully traverse the assertion in the Office Action that a "linking group of significant length" is required for the display moiety to function. Limitations on the length of a linking group between a substrate and a reactant ligand are not present in the specification or in the previous Amendment and Request for Reconsideration, filed October 28, 2003.

The specification provides both generic and specific disclosure of a variety of linking moieties, including single atom linking moieties and extended chain alkanethiol linking moieties. One skilled in the art would be able to prepare a protein chip as recited in claims 37-39 without undue experimentation. Accordingly, claims 36-39 are in full compliance with 35 U.S.C. § 112, 1st paragraph, and applicants request that this rejection be withdrawn.

C. Claims 36-39 stand rejected under 35 U.S.C. § 112, 1st paragraph, as allegedly not enabled by the specification with respect to the preparation of a reaction product of a reactant ligand and a fusion polypeptide. No additional assertions are set forth in the Office Action in support of this rejection, except for a reference to p. 13 of applicants' specification.

This rejection of claims 36-39 under 35 U.S.C. § 112, 1st paragraph, is respectfully traversed, as a *prima facie* case of non-enablement has not been made. As noted in MPEP 2164.04:

> In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention.

No reasoning or evidence has been provided in support of this rejection. If the reasoning or evidence is presumed to be present in the previous rejections in the Office Action, then these issues have been addressed above. Accordingly, Applicants request that this 35 U.S.C. § 112, 1st paragraph rejection be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 36-39 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Mrksich (Chem. Soc. Rev., 2000, **29**, 267-273) or Yousaf et al. (J. Am. Chem. Soc., **1999**, *121*, 4286-4287), in combination with the references listed in applicants' specification at page 15. The reasoning for these rejections is as set forth in the previous Office Action of May 28, 2003.

The rejection of claims 36-39 under 35 U.S.C. § 103(a) is respectfully traversed, as the cited references do not disclose or suggest each and every element of the claims. Specifically, the references do not disclose or suggest a fusion polypeptide as recited in claim 36. Applicants' specification defines a "fusion" as "a molecule comprising a capture polypeptide and a display moiety" (p. 11, lines 10-11), and defines

a "display moiety" as a polypeptide or polynucleotide (p. 11, lines 15-17). The term "capture polypeptide" is defined at p. 11, lines 12-14 as:

> ... a polypeptide, present as a fusion with the display moiety, which reacts specifically with a corresponding reactant ligand, and which forms a covalent bond with the reactant ligand.

Thus, the fusion polypeptide of claim 36 includes a display moiety and a capture polypeptide moiety, where the capture polypeptide moiety forms a covalent bond with the reactant ligand.

Mrksich, Yousaf et al., and the references listed in applicants' specification at p. 15, taken individually or in any combination, do not disclose or suggest a fusion polypeptide comprising a capture polypeptide where the capture polypeptide forms a covalent bond with a reactant ligand. Moreover, the fusion polypeptide as claimed is not addressed at all by the Office Actions in the rejection under 35 U.S.C. § 103(a). In the absence of a disclosure or suggestion of this claim element, a *prima facie* case of obviousness over the cited references has not been presented.

It is noted for the record that the Office Action's characterization of applicants' previous arguments is respectfully traversed. The present Office Action presents applicants remarks in the prior Amendment and Request for Reconsideration, filed October 28, 2003 as follows:

> Applicant basically argues that there is no motivation to substitute one specific binding ligand pair for another equivalent pair in the products of references *a)*

where "references *a)*" refers to Mrksich and Yousaf et al.. This characterization is not consistent with the text of applicants' previous remarks. Rather, applicants pointed out that the specific binding pairs cited by the Office Action are not equivalent to each other. The Office Actions have incorrectly equated the conventional Ni(II) / His-tag polypeptide system with applicants' quinone-NTA / His-tag system. This equation is not valid, particularly in view of the description of these two systems in the specification. Applicants disclose the disadvantages of the non-covalent Ni(II) / His-tag system specifically at p. 2, lines 8-18. In contrast, the listing of reactant ligand/capture polypeptide pairs in Table A on p. 15 of the specification includes only pairs that form

covalent bonds. Thus, the specific binding pairs disclosed in the references cannot be equivalent to the capture polypeptide and corresponding reactant ligand as recited in the claims. Since a valid equivalence has not been established, the burden remains on the Office to provide evidence of a suggestion or motivation to modify the references to include applicants' claimed reaction product (see MPEP 2143).

The applied references, alone or in improper combination with the references listed in applicants' specification at p. 15, do not teach or suggest a reaction product of a reactant ligand and a fusion polypeptide as claimed. The references do not disclose or suggest each and every element of the claims, nor do the references disclose or suggest any equivalent substitutions that would provide the claimed reaction product. Accordingly, a *prima facie* case of obviousness has not been presented, and applicants request that this rejection be withdrawn.

Conclusion

In conclusion, all of the grounds raised in the outstanding Office Action for rejecting the application are believed to be overcome or rendered moot based on the amendments and remarks above. Thus, it is respectfully submitted that all of the presently presented claims are in condition for allowance. Should the Examiner feel a discussion would expedite the prosecution of this application, the Examiner is kindly invited to contact the undersigned.

Also submitted at this time is a Petition For Extension Of Time for three (3) months.

Respectfully submitted,

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